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Registration Decision RD2014-07

Natamycin

(publié aussi en français)

13 May 2014

This document is published by the Health Canada Pest Management Regulatory Agency. For further information, please contact:

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Canada

ISSN: 1925-0932 (print)
1925-0940 (online)

Catalogue number: H113-25/2014-07E (print version)
H113-25/2014-07E-PDF (PDF version)

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Registration Decision for Natamycin

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is granting full registration for the sale and use of Natamycin TGAI and Zivion M (trade name for Natamycin L) containing the technical grade active ingredient natamycin, to suppress dry bubble disease in mushroom production.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

These products were first proposed for registration in the consultation document[1] Proposed Registration Decision PRD2012-14, *Natamycin*. This Registration Decision[2] describes this stage of the PMRA's regulatory process for natamycin and summarizes the Agency's decision, the reasons for it and provides, in Appendix I, a summary of comments received during the consultation process as well as the PMRA's response to these comments. This decision is consistent with the proposed registration decision stated in PRD2012-14.

For more details on the information presented in this Registration Decision, please refer to the PRD2012-14, which contains a detailed evaluation of the information submitted in support of this registration.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[3] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its conditions of registration. The Act also requires that products have value[4] when used according to label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

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1 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

2 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

3 "Acceptable risks" as defined by subsection 2(2) of *Pest Control Products Act*.

4 "Value" as defined by subsection 2(1) of *Pest Control Products Act*"...the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact".

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

What is Natamycin?

Natamycin is a substance naturally produced by the soil bacterium *Streptomyces natalensis* that inactivates germinating fungal spores.

Health Considerations

Can Approved Uses of Natamycin Affect Human Health?

Natamycin is unlikely to affect human health when it is used according to label directions.

Exposure to natamycin may occur when handling the end-use product, Zivion M, which is a fungicide to suppress dry bubble disease on button mushrooms (*Agaricus bisporus*). When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

The technical grade active ingredient, natamycin (98%), is of low acute toxicity via the oral, dermal, and inhalation routes. It is severely irritating to the eyes and slightly irritating to the skin. Natamycin is not considered a dermal sensitizer. Cautionary statements indicating the potential for eye irritation are required on the technical grade active ingredient product label. Dermal exposure is possible for workers handling the end-use product, Zivion M, and for workers engaged in post-application activities such as harvesting, clean-up and maintenance. Therefore, precautionary measures including Personal Protective Equipment (PPE) are required on the end-use product label to mitigate such exposure concerns. The potential for bystander exposure is expected to be minimal as non-workers are not expected to be present in the enclosed mushroom growing houses during the applications.

Residues in Water and Food

Dietary risks from food and water are not of concern.

Natamycin has a long history of use as a food additive to prevent spoilage by molds and yeasts, and is approved as a direct food additive in more than 70 countries. The end-use product, Zivion M, will be applied directly to the mushroom bed at casing and at pinning; however, food residue exposure is not expected to be of concern as conservative exposure estimates indicate that the proposed use of Zivion M will not appreciably increase the dietary exposure to natamycin above what is currently expected from its use as a food additive.

Therefore, the proposed use of Zivion M is not expected to result in unacceptable dietary risks when the product is used according to label instructions. In addition, as Zivion M is to be applied inside an enclosed growing house, exposure to natamycin in drinking water is not expected to occur. The PMRA has also determined that a Maximum Residue Limit (MRL) is not required for natamycin.

Occupational Risks From Handling Zivion M

Occupational risks are not of concern when Zivion M is used according to label directions, which include protective measures.

Occupational exposure to individuals handling Zivion M is not expected to result in unacceptable risk when the proposed product is used according to label directions. Precautionary and hygiene statements on the label (for example, wearing of PPE) are considered adequate to protect individuals from potential risks from occupational exposure.

Environmental Considerations

What Happens When Natamycin is Introduced into the Environment?

The proposed use of natamycin in mushroom houses is not expected to result in environmental exposure.

Natamycin is a naturally occurring substance. When used as proposed in mushroom houses, negligible amounts of natamycin are expected to enter the environment either during use or through the disposal of spent compost medium.

Value Considerations

What Is the Value of Zivion M?

Zivion M is a bio-fungicide that suppresses dry bubble disease in mushroom production. Zivion M reduces the development of dry bubble disease in commercial mushrooms. It does not affect mycelial growth, and so does not negatively affect mushroom yield.

Measures to Minimize Risk

Registered pesticide product labels include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures on the label of Natamycin TGAI and Zivion M to address the potential risks identified in this assessment are as follows:

Key Risk-Reduction Measures

Human Health

The signal words 'DANGER – EYE IRRITANT' are required on the principal display panel of the Natamycin TGAI label. The statements 'Severely irritating to the eye, DO NOT get in eyes' are required on the secondary display panel of the Natamycin TGAI label.

The personal protective equipment for all handling, clean-up and maintenance activities required on the Zivion M label includes a long-sleeved shirt and long pants or coveralls, shoes and socks, and waterproof gloves. Safety glasses are also required for mixers, loaders and applicators.

Environment

No mitigative measures are required for the proposed use of Natamycin TGAI and its end-use product, Zivion M, in mushroom growing facilities.

Other Information

The relevant test data on which the decision is based (as referenced in PRD2012-14, *Natamycin)* are available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa). For more information, please contact the PMRA's Pest Management Information Service by phone (1-800-267-6315) or by e-mail (pmra.infoserv@hc-sc.gc.ca).

Any person may file a notice of objection[5] regarding this registration decision within 60 days from the date of publication of this Registration Decision. For more information regarding the basis for objecting (which must be based on scientific grounds), please refer to the Pesticides and Pest Management portion of the Health Canada's website (Request a Reconsideration of Decision, healthcanada.gc.ca/pmra) or contact the PMRA's Pest Management Information Service.

[5] As per subsection 35(1) of the *Pest Control Products Act.*

Appendix I Comments and Responses

Comment 1 – Toxicity Classification, Personal Protective Equipment, Restricted-Entry Interval and Preharvest Interval Recommendation

The review of the technical product (Natamycin TGAI) and the end-use product (Zivion M) were conducted jointly between the USEPA and the PMRA. The PMRA received comments regarding the discrepancies between the label recommendations made by the USEPA and the PMRA. The specific comments were in relation to:

- The **toxicity classification** of the technical product (Natamycin TGAI) and the end-use product (Zivion M), specifically to the eye irritation classification – "Why does PMRA classify natamycin as causing irreversible eye damage (that is, Category I), while the USEPA classifies it as Category IV?"
- The **Personal Protective Equipment (PPE) requirement** for re-entry workers during clean-up and maintenance activities, and harvesting – Commenters asked why "Full PPE" is required throughout the production period.
- The recommended **preharvest interval and the lack of a restricted-entry interval**. The USEPA label states a 12-hour re-entry interval after application. "The PMRA identifies the entire production period after application as the pre-entry interval. On Canadian mushroom farms the entire production period could amount to 20 days from application to last harvest of mushrooms. Why does the PMRA list the entire production period of up to 20 days when the pre-entry period could be 12 hours?"

Response 1

Although the same data were reviewed and shared by both agencies, the risk assessments were conducted independently. The required label statements for the Canadian registration are based on the PMRA risk assessment.

For the Natamycin TGAI, the PMRA's classification takes into account the highest level of irritation elicited by the technical grade active ingredient. Therefore, based on the toxicity profile of Natamycin TGAI, it is classified as "severely irritating" to the eyes, by PMRA criteria. For this classification, the warning label statements "DANGER - EYE IRRITANT" and "Severely irritating. DO NOT get in eyes" are required.

The primary eye irritation study submitted for Zivion M categorizes it as non- to minimally irritating to the eyes, thus protective eyewear would not normally be required for the end-use product. However, information provided by the applicant in the use description stated safety glasses are worn during re-entry activities, as such, the PMRA has recommended them on the proposed label. Based on the comments received, the PMRA accepts that wearing safety glasses is not a standard practice for re-entry workers in mushroom houses and has no objection on the removal of protective eyewear for harvesters and for re-entry workers.

The PMRA recommended PPE only for workers directly handing Zivion M during application clean up and maintenance activities. The PMRA does not require restricted-entry interval for Zivon M. Postapplication activities identified by the applicant are harvesting and data gathering, which would include temperature and carbon dioxide measurements/monitoring. The only postapplication activity identified by the applicant that would require PPE is harvesting. It is anticipated that wearing a long-sleeve shirt, long pant and chemical-resistant gloves during this

activity will not pose an issue. Comments received have specifically mentioned that wearing gloves during harvesting is a standard food safety practice. The other post-application activity such as data gathering would not require PPE. With the removal of the protective eyewear for harvesters, the PPE requirement is essentially the same between the USEPA and the PMRA for Zivion M.

A preharvest interval of four days is required on the label, and this is consistent with the USEPA.

Comment 2 – End-use Product Formulation and Use Pattern
The PMRA received several comments on Zivion M, specifically on how the product is applied (for example, hand wand versus irrigation system) and the discrepancies with respect to the use pattern between the American and Canadian labels (4 versus 2 applications), which may result in the Canadian users being at a disadvantage.

Response 2
As stated in the PRD2012-14, the end-use product is a liquid, to be diluted in water and applied with a hand wand to the surface of the prepared mushroom bed as a surface drench, once at casing and once at pinning. The first application is to be made at casing, prior to the emergence of fruiting bodies, as per the proposed label directions. Treatments were applied to the substrate using a hand-held sprayer in efficacy trials. Application through irrigation systems was not assessed as it was not on the proposed label as a method of application.

In addition, the original label submitted with the application indicated that four applications may be made; however, that two applications, one at casing and one at pinning, may provide adequate control. This was also repeated in supporting documents provided by the registrant (2010, DACO 10.1 Value Summary). Efficacy data showed no difference in the level of control observed with two applications compared to four applications (2009, Screening of Delvocid Liquid 05096 against *Verticillium fungicola*; 2009, Influence of Natamycin L on Mushroom Production). The value of four applications was not demonstrated, so the use pattern of Zivion M was amended to two applications.

Please note that Zivion M was assessed before the publication of PRO2010-06 – *Value Guidance – Benefit Information and Use History*. Under current standards, efficacy data can be supplemented with value information in the form of scientific rationales, benefits analysis and history of use information to support registration of new products or amendments to registered products. The PMRA will consider amendments to the use pattern in a future application with the submission of value information supporting the amendment.

Comment 3 – Resistance
A comment was made regarding Zivion M being a low-toxicity, biopesticide with no evidence of acquired resistance by the dry bubble organism.

Response 3

The PMRA acknowledges that there is no known resistance to natamycin by the dry bubble pathogen or any other organism exposed to natamycin. Based on the mode of action of natamycin, resistance is not expected. It is advised that Resistance Management practices are employed to prolong or prevent the development of possible resistance mechanisms. Currently, the Fungicide Resistance Action Committee has not established guidelines for natamycin. Generally, practices such as product rotation and/or tank mixing with other modes of action are recommended to manage resistant pathogen populations.